REMARKS

Claims 21-36 are in this application, the specification and claim 21 having been amended, claim 30 having been cancelled, and no claims having been added, by this response. The specification was objected to, and claims 21-36 were rejected under 35 USC 112, ¶¶1 and/or 2.

The amendment

The amendment to the specification at page 16, paragraph at lines 8-16, adds a reference to US Patent No. 6,458,998 to parallel the reference to WO 00/71506. No new matter is added by this amendment because the application as filed already referred to US Application No. 09/579,279 and that application issued as US Patent No. 6,458,998 – the reference is found at page 3, line 28 of the present application as filed, and note that the reference to the US Patent was added in the amendment accompanying the Request for Continued Examination. Nor is there any new matter added in incorporating that patent by reference, because the application was already incorporated by reference at page 3, lines 28 and 29.

The amendment to the claims incorporates the subject matter of (now-cancelled) claim 30 into claim 21.

The objection to the specification

The specification was objected to as incorporating essential material by reference to a foreign application or patent or publication. Although the Office Action did not state what material was considered essential, Applicants assume it to be the same material that was rejected as new matter when presented in claims 21-22 and 30-36 (see the Office Action and response below).

This objection is respectfully traversed.

Although Applicants had originally referred, in the response mailed 4 April 2003, to WO 00/71506, and accept that if the material incorporated by reference were considered essential they would have been required to amend the disclosure of the application to include the material incorporated by reference, Applicants note that they may also refer to the '279 application as the source of the amendment. The incorporation by reference of the '279 application is seen at page 3, lines 28-29; and this application has been patented as the '998 patent. Applicants submit that, even if the material incorporated by reference is considered essential, because the material is incorporated by reference to a US patent, the application referred to having issued as a patent after the filing of this application, incorporation by reference is proper (MPEP 608.01(p) I.A.1., second paragraph – the Office has a copy of the '998 patent), so that no amendment of the disclosure to include the material incorporated by reference is required.

Withdrawal of the objection is respectfully requested.

The 35 USC 112, ¶1 "written description" rejection

Claims 21-22 and 30-36 were rejected under 35 USC 112, ¶1 "as containing subject matter which was not described in the specification ... ". The Office Action asserts that the amendment accompanying the RCE and adding claims 21-36 "is deemed to insert <u>new matter</u> into the claims since the specification as originally filed does not provide support for those compounds having Formula I <u>in particular when Y is now newly defined as in claim 21</u> and those <u>particular compounds subgenus and species) in claims 22</u> being useful in the instant method ... ". (Emphasis in original).

The Office Action acknowledges that the genus of claim 21 and subgenus of claim 22 are taught by US Patent 6,458,998 which is incorporated by reference, but says that this patent "merely discloses these compounds including subgenus and species themselves in claims 21-22 and their use

in the methods of stimulating the kinase activity of the insulin receptor, activating the insulin receptor, and stimulating the uptake of glucose, but the patent within the four corners does not fairly provide the support for these particular subgenus and species being useful in the instant method of treating a metabolic disorder in a person induced by the treatment of the person with an HIV protease inhibitor."

Applicants respectfully disagree.

With respect at least to written description, the specification of this application as filed discloses that insulin receptor-activating compounds in general are useful in the method of the invention (*see, e.g.*, the first paragraph of the Summary of the Invention at page 3), and therefore provides support for the method of treating a metabolic disorder in a person induced by the treatment of that person with an HIV protease inhibitor by administering any insulin receptor-activating compound or group of compounds. A disclosure that all compounds of a category are useful is *ipso facto* a disclosure that any such compound or group of compounds within that category are useful: it is no more than a restatement of the old syllogism "All men are mortal. Aristotle is a man. Therefore Aristotle is mortal.", replacing "men" with "insulin receptor-activating compounds", "mortal" with "useful in the method of this invention" and "Aristotle" with "the compounds of claim 21 (or 22)".

Further, the specification of this application as filed discloses that the compounds of Formula I are useful in the method of the invention, and the specification further discloses that these compounds are disclosed in US Application No. 09/579,279 (Patent No. 6,458,998), reinforcing the logical conclusion that any chosen compound or group of compounds within Formula I is useful in the method of the invention.

Because US Patent No. 6,458,998 is incorporated by reference, it is equivalent in terms of its support for the claims of this application to disclosure in this application itself – this is the essence of incorporation by reference. Applicants are therefore entitled to use the disclosure of that patent for the selection of any group (genus, subgenus, species) disclosed by that patent, just as if that group were disclosed by the application itself.

The Office Action notes that "a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads", referring to *In re Smith*.

Applicants do not disagree with that proposition; however, that is not the situation here: no new subgenus is being created. As pointed out in the remarks accompanying the RCE, the disclosure of US Patent No. 6,458,998 provides clear support for the genus of compounds claimed in claim 21 and subgenus claimed in claim 22: these are a disclosed (supported) genus and subgenus. Since all the compounds of formula I are disclosed explicitly in this application as being useful in the method, the genus of claim 21 and subgenus of claim 22 are also inherently disclosed as being useful in the method.

Applicants therefore submit that there is within the instant specification (including the disclosure of US Patent No. 6,458,998, which is incorporated by reference and is therefore a part of the specification) information which would lead the artisan in the field to believe that Applicants were in possession of the invention of claims 21, 22, and 30-36.

With respect to the non-compound limitations of claims 30-36, these come directly from claims 2 and 12-16 of the application as filed.

Withdrawal of the rejection is requested.

The 35 USC 112, ¶1 "enablement" rejection

Claims 21-36 were rejected under 35 USC 112, ¶1 "because the specification, while being enabling the instant compounds for treating particular metabolic disorders or particular side effects (for example in claims 30-31) in a person induced by treatment with the particular known HIV protease inhibitor such as ritonavir, indinavir, amprenavir (see page 29 of the specification) does not reasonably provide enablement for treating **any** metabolic disorders which read on any disorders/disease in a person induced by treatment of the person with **any** HIV protease inhibitors encompassing any known and unknown HIV protease inhibitors. Moreover, the specification, while being enabling the particular additional form of treatment for insulin resistance, hyperglycemia, and disorders in claim 31 for the method of treatment herein, does not reasonably provide enablement for treating **any** agents represented by an additional form of treatment for insulin resistance, hyperglycemia and disorders herein." (emphasis in the original).

With respect to the metabolic disorders, Applicants have amended claim 21 to limit to the particular metabolic disorders set out in now-cancelled claim 31, namely insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, or hypertriglyceridemia, which the Office Action agrees are enabled.

With respect to the HIV protease inhibitors and the additional form of treatment, Applicants respectfully disagree that the enablement is limited only to the exemplified protease inhibitors and additional forms of treatment. With respect to the protease inhibitors, the rejection goes to all of claims 21-36; with respect to the additional form of treatment, the rejection goes only to claims 31, 32, 35, and 36, since claims 33 and 34 specifically refer to insulin as the additional form of treatment.

The Examiner refers to the factors used by the Court of Appeals for the Federal Circuit in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), reversing a PTO finding that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement, and recites the factors in the order given in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Taking the *Wands* factors in the order recited in the Office Action:

1) The nature of the invention

Applicants agree that the invention is a method of treating a metabolic disorder in a person induced by the treatment of that person with an HIV protease inhibitor, where the metabolic disorder is insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, or hypertriglyceridemia. Thus the invention is a method of treatment.

2) The state of the prior art

The art recognizes that HIV protease inhibitors have been found to induce insulin resistance and other related disturbances in metabolism, and that this appears to be a class effect in all currently available HIV protease inhibitors. The art also recognizes that at least three of these compounds inhibit the glucose transporter, hence inhibiting glucose uptake into cells.

The art also recognizes that insulin receptor-activating compounds exist and are known to stimulate the uptake of extracellular glucose; and that several classes of compounds are known to be insulin receptor-activating compounds. This application, incorporating by reference US Patent 6,458,998, demonstrates that the compounds of claim 21 and dependent claims are insulin receptor-activating compounds.

3) The relative skill of those in the art

Applicants agree that persons of ordinary skill in the art of this invention will have a high level of skill.

4) The breadth of the claims

The claims are limited to treating one or more of a set of metabolic disorders known to the art to be induced by HIV protease inhibitors (*see* paragraph 2) above) in a person in whom these disorders have been induced by treatment with an HIV protease inhibitor, by administering a particular insulin receptor-activating compound (a compound of claim 21), and optionally (claims 31-36) also administering an additional form of treatment for the metabolic disorder.

The Office Action asserts extreme broadness of the claims in reading on any metabolic disorder induced by any HIV protease inhibitor and any additional treatment. But this does not constitute great breadth.

First, the claims have been limited to only the metabolic disorders listed in the specification and formerly claimed in claim 31 - disorders known to the art to be produced by HIV protease inhibitors.

Second, whether a currently known HIV protease inhibitor or new and as yet unknown HIV protease inhibitor induces the metabolic disorder is irrelevant – the only issue is if the metabolic disorder is induced by the HIV protease inhibitor, then it is treated by the method of the invention, and this is what is asserted and what the Office Action has failed to cast reasonable doubt on. If a new HIV protease inhibitor induces the disorder, then the disorder will be treated by the method of the invention; if a new protease inhibitor is found that does not induce the disorder, then the disorder does not exist in the person and is not treated by the method of this invention, and the claims are not implicated. The fact that the HIV protease inhibitor is claimed functionally (as an HIV protease inhibitor, rather than by chemical class) does not affect this or add any breadth. It is not the genus of HIV protease inhibitors that is being claimed, it is a method of treatment of their side effects, and those side effects are claimed by name not function.

Third, whether a disclosed, a currently known but not disclosed, or an as yet unknown additional treatment for the now-claimed metabolic disorders is used is also irrelevant – the only issue (as it relates to claims 31-36) is whether a treatment for the metabolic disorder other than treatment with the claimed insulin receptor-activating compounds is also administered. Claims 31-36 are narrower than claim 21: they recite that an additional treatment may also be administered. If the disorder is induced by treatment with an HIV protease inhibitor and treated with the method of this invention, then it can also be additionally treated with other therapies for the disorder. The fact that the additional treatment is claimed functionally (as an additional treatment, rather than by chemical class) does not affect this or add any breadth. It is not the genus of additional treatments that is being claimed, it is their use in conjunction with the claimed method of treatment.

5) The amount of direction or guidance provided

The clamed method is described in the Detailed Description of the invention for example at page 18, line 15 to page 21, line 3. A person of ordinary skill in the art would have no difficulty, considering the disclosure in the application and their knowledge, in carrying out the method. Routes of administration and dosages are discussed, as are representative additional methods of treatment that might be used, such as the administration of insulin, or an insulin analog, or a non-insulin antidiabetic agent such as a thiazolidinedione or sulphonylurea.

The Office Action criticizes the claims for "functional language at the point of novelty". But in fact the claims do not contain functional language at the point of novelty: the novelty of the claims does not lie in the HIV protease inhibitors or in the additional forms of treatment (admittedly both defined in functional terms), but in the method of treatment itself, which does not contain functional language – it is just administering a compound of the invention, which is defined by structure, to treat a named set of disorders.

6) The predictability of the art

The art recognizes that current HIV protease inhibitors induce certain metabolic disorders, such as insulin resistance, in persons treated with them. It is predictable that future HIV protease inhibitors may also do so – and in any event, if they do not, then the claimed method is not implicated because there will be no such disorder to treat.

The art recognizes the existence of insulin receptor-activating compounds, of which the compounds claimed in the claimed method are members. From the disclosure of this application, supplemented by the disclosure of US Patent No. 6,458,998 incorporated by reference, it is clear that the compounds claimed for use in the method are insulin receptor-activating compounds. It is predictable from those compounds tested that all compounds within the genus claimed would possess the property of being an insulin receptor-activating compound and would therefore be useful in the claimed method.

Finally, the art recognizes that there exist various forms of treatment for the metabolic disorders when not associated with HIV protease inhibitor treatment, such as treatment with insulin, with insulin analogs, and with non-insulin antidiabetic agents such as thiazolidinediones and sulphonylureas. Since Example 3 shows how insulin receptor-activating compounds act to reverse the HIV protease inhibitor-induced blockage of glucose uptake, it is predictable that these compounds would act with insulin or alternative additional forms of treatment to treat the disorders.

The Office Action asserts the unpredictability of therapeutic effect and risk of side effects when administering the combination of the insulin receptor-activating compound, the HIV protease inhibitor, and possibly also the additional form of treatment. With respect, this is not the province of the USPTO but of the FDA. It is already the case that persons are administered HIV protease inhibitors and that these cause the metabolic disorders noted. It is reasonable for physicians to administer insulin receptor-activating compounds in the methods of this invention to try to ameliorate these side effects, because it has been demonstrated that these compounds reverse the HIV protease inhibitor-induced blockage of glucose transport in adipocytes and are therefore predicted to ameliorate the side effects in humans. Applicants have provided sufficient reason to believe that this is likely to be beneficial and mere quotation of general warning of the risk of drug-drug interactions does not cast sufficient doubt on this predictability to negate patentability. *See In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "it is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble of supporting his presumptively accurate disclosure."

7) The presence or absence of working examples

As is conventional with patent applications in the pharmaceutical art, this application does not contain a working example of the claimed method (i.e. a clinical test in humans), but relies instead on predictive testing. Example 3 is a example that is predictive of the success of the claimed method: in the example, it is demonstrated that a compound of the invention (and another insulin

receptor-activating compound originally claimed but now restricted out) reverse the HIV protease inhibitor-induced blockage of glucose transport in adipocytes. This test is considered predictive of the efficacy of the claimed method, and the Office Action fails to raise a reasonable doubt about its predictive value.

8) The amount of experimentation necessary

To carry out the claimed method — to treat one of the claimed metabolic disorders when induced by treatment with an HIV protease inhibitor, a physician simply ascertains the presence of the claimed disorder in the patient, ascertains whether the patient has been treated with an HIV protease inhibitor, and administers one of the claimed insulin receptor-activating compounds to treat the disorder. The claimed method is simply the administration of the claimed insulin receptor-activating compound once the prerequisites are satisfied: there is no experimentation required to find out what the claimed method is.

The Office Action asserts that "the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims." (Emphasis in the original). This is not the proper test for compliance with the enablement requirement: the test is whether the application provides all information necessary for a person of ordinary skill in the art to practice the claims without undue experimentation. The application provides unequivocal guidance as to the disorders claimed to be treated and how they are to be treated, namely by administration of a compound within a class defined chemically. This administration may be accompanied by administration of an additional form of treatment for the disorder, and such additional treatments will be recognized by a person of skill in the art having regard to that knowledge and this disclosure.

Applicants respectfully submit that the specification provides all information needed for the person of ordinary skill in the art to practice the claims without undue experimentation, and that claims 21-36 are therefore enabled by the specification.

Withdrawal of the rejection is requested.

The 35 USC 112, ¶2 rejection

Claims 32 and 34-36 were rejected under 35 USC 112, ¶2 for indefiniteness over the use of the terms "insulin analog" and "less than the amount of the additional form of treatment".

The term "insulin analog" is seen in claims 35 and 36. The Office Action states that this term renders the claim indefinite because the term is not defined in the specification, so that a person of ordinary skill in the art could not ascertain the metes and bounds of the claim.

Applicants respectfully disagree.

Although the term "insulin analog" is not itself defined in the specification, Applicants are entitled to rely on the skill of the art in construing the term. Applicants believe there is no doubt as to the term "insulin" – the compound is well-defined. As to the term "analog", any dictionary gives a definition, all of them saying, more or less, "something that is similar": thus, Microsoft's Encarta gives one definition: "**similar chemical:** a chemical with a similar structure to another but differing slightly in composition." and CancerWeb's on-line dictionary offers as one of its two definitions "2. A compound that resembles another in structure but is not necessarily an isomer (e.g., 5-fluorouracil is an analog of thymine); analogs are often used to block enzymatic reactions by combining with enzymes (e.g., isopropyl thiogalactoside vs. lactose)." Thus, a person of ordinary skill in the art would clearly understand that an "insulin analog" *as that term is used in the specification and claims* (which is the requirement for definiteness – the term is not construed in the abstract)

means a compound that is either chemically similar to insulin and/or is functionally similar to insulin in terms of its biological effects.

Applicants submit that a person of ordinary skill in the art would be able to ascertain whether a compound was an "insulin analog" for the purposes of claims 35 and 36 by considering its chemical structure and biological effect; so that the metes and bounds of claims 35 and 36 are ascertainable to a person of ordinary skill in the art and the claims are definite.

The term "less than the amount of the additional form of treatment" is seen in claims 32, 34, and 36. The Office Action states that this term renders the claim indefinite "since 'less' is a relative term."

Applicants respectfully disagree.

Applicants agree that the term "less" is relative, but disagree that this introduces any indefiniteness into the claims: there is no inherent indefiniteness in the use of relative terms. The term "less" must not be construed in the abstract, but must be construed in the context of the specification and of the claims in which it appears.

Considering claim 32, which is representative of the three claims: the claim is to a method of treating a person suffering from a metabolic disorder selected from insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, or hypertriglyceridemia when that disorder is induced by treatment of the person with an HIV protease inhibitor, where the treatment comprises administration of both a therapeutically effective amount of an insulin receptor-activating compound of the genus set out in claim 21 and of a therapeutically effective amount of an additional form of treatment used for the disorder, and where the therapeutically effective amount of the additional form of treatment is less than the amount of the additional form of treatment that would be therapeutically effective if delivered alone.

This is a completely understandable situation, and in no way indefinite: if a therapeutically effective amount of aspirin to cure a headache were three tablets, and if when ibuprofen was also administered, then only two aspirin tablets were required to cure the headache, then clearly the therapeutically effective amount of aspirin required to cure the headache when ibuprofen was also administered would be less than the amount of aspirin that would be therapeutically effective when administered alone – one less tablet is required; and no-one would find this indefinite.

So what is claimed in claim 32 is that when the insulin receptor-activating compound is used as a part of the treatment of the metabolic disorder, supplementing the "additional form of treatment", the amount of the "additional form of treatment" that is required for therapeutic efficacy is reduced below that which would have been needed if the "additional form of treatment" were administered alone. The same situation is presented in claims 34 and 36, the only difference being that in those claims what constitutes the additional form of treatment is defined.

Applicants submit that a person of ordinary skill in the art would be able to ascertain whether the therapeutically effective amount of the additional form of treatment was less when an insulin receptor-activating compound was also administered than when the insulin receptor-activating compound was not, so that the metes and bounds of claims 32, 34, and 36 are ascertainable to a person of ordinary skill in the art and the claims are definite.

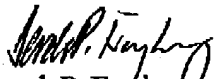
Withdrawal of the rejection is requested.

Conclusion

Applicants submit that the amended specification and claims are fully supported by the application as filed (including the disclosure of US Patent No. 6,458,998, incorporated by reference), that the specification does not contain any essential material incorporated by reference to documents other than a US patent, that no new matter is presented in claims 21-36, and that the claims as amended comply with both the written description and enablement requirements and are definite. Re-examination and allowance of claims 21-36 are respectfully requested.

Applicants reserve the right to file divisional and/or continuation application(s) to the subject matter canceled in this and previous responses.

Respectfully submitted,



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